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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,149	04/26/2000	Nicholas Nicolaides	01107.00004	1171

7590 08/10/2004  
Banner & Witcoff Ltd  
1001 G Street N W  
Washington, DC 20001-4597

EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

6415

## Office Action Summary

**Application No.**

09/558,149

**Applicant(s)**

NICOLAIDES ET AL.

**Examiner**

Ram R. Shukla

**Art Unit**

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 60-62, 70-75 and 81-87 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 60-62, 70-75 and 81-87 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on 26 April 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5/24/04.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

### **DETAILED ACTION**

1. Applicants' amendments and response filed 5/24/04 have been received.
2. Claims 14, 19, 20, 29, 53 and 59 have been canceled.
3. New claims 81-87 have been entered.
4. Claims 60-62, 70-75 and 81-87 are pending and under consideration.

### ***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 14, 19, 20, 29, 53, 58-62, 69-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: (i) a transgenic mouse in whose all germ and somatic cells a polynucleotide encoding a dominant negative allele of a PMS2 mismatch repair gene disclosed in SEQ ID NO 1 is integrated, wherein said dominant negative allele comprises a truncation mutation and wherein said dominant negative allele of said PMS2 causes a mismatch repair defect in the cells of the transgenic mouse, and wherein cells and tissues of said transgenic mouse have defect in mismatch repair; (ii) a method of making said transgenic mouse, wherein said method comprises introducing into a mouse fertilized egg a polynucleotide comprising a nucleic acid sequence encoding a dominant negative allele of PMS2 mismatch repair gene disclosed in SEQ ID NO 1, wherein said dominant negative allele of said PMS2 causes a mismatch repair defect, implanting the fertilized egg comprising the polynucleotide into a pseudopregnant female mouse, whereby the fertilized egg develops into a mature mouse and wherein cells and tissues of said transgenic mouse have defect in mismatch repair, does not reasonably provide enablement for other embodiments

of the claimed invention for reasons of record set forth in the previous office actions of 7-5-01, 3-26-02, 12-28-02, 6-16-2003 and 1-5-04. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

### ***Response to Arguments***

Applicant's arguments filed 5/21/04 have been fully considered but they are not persuasive to obviate all the grounds of rejection.

Applicants have argued that a prima facie case of non-enablement of claims 60-62, 70-87 has not been made. First, claims 70-87 are not pending, only claims 70-75 and 81-87 are pending. Second, contrary to applicants' arguments, a prima facie case of non-enablement for the full scope of the claimed invention has been made. Applicants' arguments that the office has supplied no evidence or reasonable basis to support the rejection. In response, it is reiterated that USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise. Further, applicants are referred to the office actions of 7-5-01, 3-26-02, 12-28-02, 6-16-03, 11-15-03 and 1-5-04. For example, page 4, last paragraph of the office action of 7-5-01 discussed as to how mouse and rat made with the same construct did not have the same characteristics, which indicated that even when same construct was used, the transgenic animal produced was unpredictable. In the instant case, claimed invention encompasses any dominant negative allele of a PMS2 mismatch repair gene comprising any truncation mutation and applicants' specification does not provide any guidance as to what would be the phenotype of such mice and therefore, an artisan would not know how to use these mice. As discussed in the previous office action of 1/5/04, the claimed invention encompasses making a transgenic mouse with certain characteristics or phenotype using different

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constructs comprising nucleic acid from any organism and in view of the unpredictability of the transgenic technology, an artisan would not have been able to make such transgenic mice without undue experimentation. Applicants' arguments that Dr. Kline's supplemental declaration that one of skill in the art could readily identify transgenic animals having hypermutable phenotype because the animals exhibit microsatellite instability are not persuasive because Dr. Kline's supplemental declaration does not provide any evidence that when the art of producing a transgenic mouse with a certain phenotype was unpredictable, how could one make such a mouse with all the constructs encompassed by the claimed invention. Applicants citation of US patents 5,614,396 or 6,586,655 or printed application 2002/0038467 do not provide enabling disclosure for the instant invention because the instant application does not teach using the methods used in these patents. Applicants' amendment of claims 61 and 71 do not address the enablement issues discussed in the previous office actions and as discussed above. It is noted that applicants except for arguments did not provide any evidence to demonstrate that making of a transgenic mouse with transgenes comprising any dominant negative PMS2 from any organism with a certain characteristic in view of the unpredictability of the art of transgenesis. Applicants' argument alone cannot take place of evidence lacking in the record (see *In re Scarbrough* 182 USPQ, (CCPA) 1979).

7. In view of applicants' statement that claims 13-18 and 45-50 of the co-pending application 09/953,646 have been canceled, the double patenting rejection of the pending claims has been withdrawn.

8. No claim is allowed.

9. The Allowable subject matter indicated in the previous office action of 1/5/04 is reiterated below:

(i) A transgenic mouse in whose all germ and somatic cells a polynucleotide encoding a dominant negative allele of a PMS2 mismatch repair gene disclosed in SEQ ID NO 1 is integrated, wherein said dominant negative allele comprises a

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truncation mutation and wherein said dominant negative allele of said PMS2 causes a mismatch repair defect in the cells of the transgenic mouse, and wherein cells and tissues of said transgenic mouse have defect in mismatch repair;

(ii) a method of making said transgenic mouse, wherein said method comprises introducing into a mouse fertilized egg a polynucleotide comprising a nucleic acid sequence encoding a dominant negative allele of PMS2 mismatch repair gene disclosed in SEQ ID NO 1, wherein said dominant negative allele of said PMS2 causes a mismatch repair defect, implanting the fertilized egg comprising the polynucleotide into a pseudopregnant female mouse, whereby the fertilized egg develops into a mature mouse and wherein cells and tissues of said transgenic mouse have defect in mismatch repair; and

(iii) a method of using said transgenic mouse.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

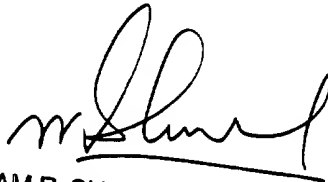
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or

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proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.  
Primary Examiner  
Art Unit 1632



RAM R. SHUKLA, PH.D.  
PRIMARY EXAMINER